Crystallization

W. Beckmann and U. Budde, Schering AG, Berlin, Germany

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Two decades ago, crystallization was called both an art and a science. However, the field is improving quickly. The crystallization of pharmaceuticals is still sometimes regarded an art and rather a mystery. However, crystallization processes are widely used throughout the production processes of the active ingredient of a drug product, and a lot of knowledge is nowadays available.

For the crystallization of drug substances several aspects have to be considered, as the crystallization process is the last step in the chemical manufacture of pharmaceuticals. The crystallization determines a number of important properties of the drug substance, namely the purity and residual solvent content, the polymorphic form, crystal size and size distribution, and it affects downstream processes such as drying, ease of comminution and formulation of the final drug product.

The crystallization of all drug intermediates have the same goals and follows the same procedures as for other organic substances and thus will not be discussed here separately.

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General Considerations for the Development of the Crystallization Process

In general, the demands on the crystallization of a drug substance differ according to the final use, e.g. if the product is used in oral dosage forms, in ointments or in liquid formulations. However, for the sake of simplicity, it is assumed here that the crystallized drug substance is to be used in an oral dosage form.

Figure 1 shows a typical crystallization process of a drug substance and the downstream processes up to the formulation of the drug product. The crystallization and the properties of the product have a great influence on all the following steps.

Impurities

Foreign and related compounds The requirements on the purity of a drug substance are strict; guidelines require a purity of typically >98%. Individual impurities with a known structure have to be below 0.5% and unidentified impurities have to be below 0.1 or 0.05%. In addition, the toxicological effect of all impurities must have been assessed in the first toxicological tests, i.e. no new impurity is allowed that has not been present in the batch used for toxicological experiments.

The purification of a drug substance via crystallization cannot be predicted easily. While foreign impurities can mostly be easily reduced, related substances like impurities stemming from side reactions in the synthesis behave in an unpredictable way. In general, the purification via crystallization will decrease with an increase in the yield, especially if the yields are >90–95%.

Residual solvent content Beside obvious solvent properties such as a certain solubility for the drug substance and an appropriate purification to yield ratio, the choice of the solvent for the crystallization of a drug substance is governed by the permissible limitations placed on the residual solvent content of the drug substance. All typical solvents have been classified according to their toxicity and tolerated daily uptakes of a solvent have been established, that are not to be exceeded by the drug product.

Three classes of solvents are distinguished: (i) those that should be avoided; (ii) those that have a limit to their daily uptake; and (iii) those for which no limits have been set up so far. Examples are benzene and dichloroethane for class 1, methanol and dichloromethane for class 2 and ethanol, ethyl acetate and acetone for class 3. In addition, good manufacturing practice (GMP) requires the manufacturer to limit the residual solvent to the lowest content possible.

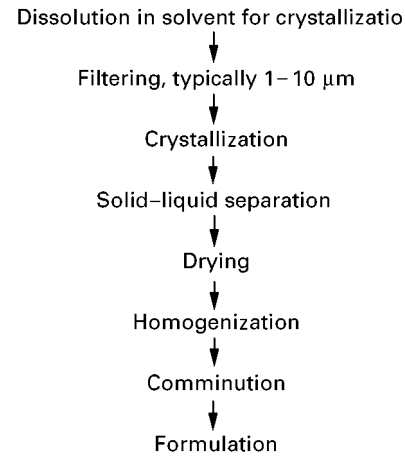

Figure 1 Typical crystallization and downstream processes up to formulation.

Table 1 Productivity, yield and development prerequisites for the separation of isomers via crystallization, enzymatic resolution and chromatography

Parameter	*Crystallization*	*Enzymatic resolution*	*Chromatography*
Productivity	High	Low	Medium
Selectivity	Varies	High	Very high
Prerequisite	High	High	Low
Development time	High	High	Low to medium

Two types of limits for the residual solvent content of a drug are distinguished. Case 1 is a dosage-independent concentration limit and Case 2 is a limit for the total uptake through the drug product, that must not be exceeded by the solvent content of the drug substance and the excipients.

The mechanisms of incorporation of solvent into the crystals can be described as follows:

- The solvent is incorporated into the lattice at fixed positions during the crystallization (solvate formation). In this case, the incorporation cannot be avoided directly. In some cases, a solvent of crystallization is removed or replaced by water.
- The solvent is incorporated into the lattice as three-dimensional inclusions. The formation of inclusions is facilitated by the speed of crystallization, thus, the amount of residual solvent can be decreased by lowering the rate of crystallization. For some systems, the tendency to form three-dimensional inclusions of solvent increases with the crystal size.

If a problem with the residual solvent content of a drug arises, the clear remedy is a change of solvent.

Separation of isomers An increasing number of pharmaceutical active ingredients are either isomers or enantiomers. Typically, different isomers of a chemical compound exhibit different biological or therapeutic activities, with one of the isomers being the carrier of the activity. In some cases, the second isomer can even have an adverse biological activity. In any case, the inactive isomer constitutes an unnecessary load to the body. Thus, a separation of isomers is almost a prerequisite for the production of a drug.

Isomers can be separated by enzymatic resolution, chromatography or crystallization. **Table 1** summarizes and compares productivity, yield and development prerequisites of the three separation techniques.

The success (or possibility) of the separation of isomers via crystallization depends on the phase diagram of the two compounds.

Figure 2 shows typical phase diagrams of isomers, i.e. eutectics, solid solutions and partial solubility in the solid state. A separation of isomers in a single step is only feasible for eutectic systems. Systems forming solid solutions have to be purified in multiple steps, as for example in zone refining which is only feasible if the substance is stable in the molten state. For systems exhibiting partial miscibility in the solid state, the separation cannot be better than the partial miscibility concentrations.

In principle, isomers forming eutectics can be separated directly via crystallization. However, without using special techniques, the crystallization can only be carried out until the concentration of the mother liquor has reached the composition of the eutectic mixture. To improve the yield two ways are often pursued:

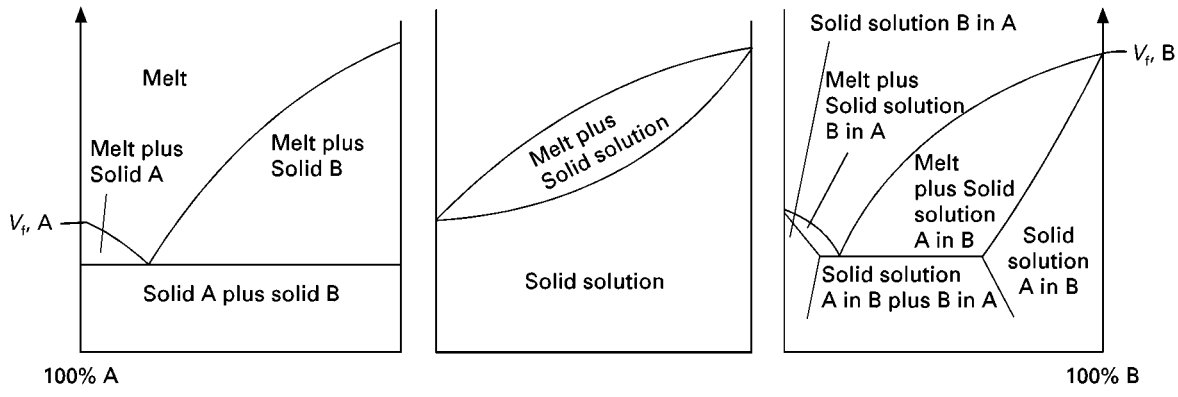
Melt
Melt plus Solid A
Melt plus Solid B
V_f, A
Solid A plus solid B
Melt plus Solid solution
Solid solution
Solid solution B in A
V_f, B
Melt plus Solid solution B in A
Melt plus Solid solution A in B
Solid solution A in B
Solid solution A in B plus B in A
100% A
100% B

Figure 2 Typical phase diagrams for isomers: eutectics, complete miscibility in the solid state and partial miscibility in the solid.

- Forming diastereomeric salt derivatives of the isomer will often direct the eutectic composition towards one of the isomers. This will increase the yield and productivity of the crystallization process considerably.
- The desired isomer is enriched via preparative HPLC followed by crystallization. The chromatographic technique achieves a high degree of enrichment but the amount of solvent to be handled is considerable. Crystallization is carried out at high concentrations and thus more effectively. Attempts have been made to find the optimal cost effective division between the separation via preparative HPLC and crystallization.

Solid-State Forms

Polymorphism Before a crystallization process is developed, the solid-state polymorphism of the substance has to be elucidated. Less than 50% of the drug substances described in monographs crystallize in a single polymorphic form; the majority form polymorphs, pseudomorphs, or both. The polymorphic form of a drug can influence a number of its properties such as the following:

- The solubility and the dissolution rate and consequently the bioavailability. Although typical differences in solubility between polymorphs are of the order of ≤ 2, the differences in solubility between pseudomorphs are somewhat higher. The largest differences exist between amorphous and crystalline material.
- The habit (the external appearance) of the crystals which in turn influences the mechanical properties of the drug during further processing such as the ease of comminution.
- The chemical stability.

Thus the regulatory agencies ask for the reproducible production of the specified polymorphic form. In the case that a drug can form more than one polymorph, a choice of the polymorphic form must be made.

Amorphous compounds Amorphous solids are a metastable form of the drug substance that can crystallize at any instant. In this respect, an amorphous form can only be second choice as solid-state form for a drug substance.

The stability of amorphous material can be characterisized by its glass-transition temperature T_g, which can be determined by differential scanning calorimetry (DSC). Below the glass-transition temperature, the molecules are practically frozen; above it they have a finite mobility making the conversion into a crystalline form possible.

The glass-transition temperature and thus the stability of amorphous materials can be decreased by residual solvent.

Salts A number of properties of the chemical compound can call for the use of a salt as the drug substance. An insufficient chemical stability of the parent compound can be overcome by the formation of a salt, e.g. amines sensitive to oxidation can be stabilized by forming a hydrochloride. Other properties calling for salt formation include low melting points or unfavourable solid-state properties such as a tendency to form amorphous material or too many polymorphs.

Finally, in case of an insufficient solubility in water or gastro-enteric fluids it is sometimes tried to avoid this problem by the formation of salts.

Salts of sparingly-soluble parent compounds can lead to the precipitation of the parent compound when the salt is dissolved in water. This poses considerable problems if it occurs during formulation like wet granulation.

Salts are typically formed by precipitation or reaction crystallization, i.e. by adding an acid or a base to a solution of the drug substance. Of course, each salt constitutes a new drug substance, that has to be treated accordingly as a new chemical entity.

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Clathrates Chemical instability of parent compounds can also be overcome by the formation of clathrates typically of α-, β- or γ-cyclodextrin. The parent molecule partially enters the large voids of the cyclodextrin (see **Figure 3**). It is thus shielded from the environment, especially the excipients.

The clathrate is typically formed by precipitation i.e. by adding the parent compound dissolved in a water-miscible organic solvent to an aqueous solution of the cyclodextrin.

Choice of solid-state form The selection of the optimal solid-state form is an important step in the

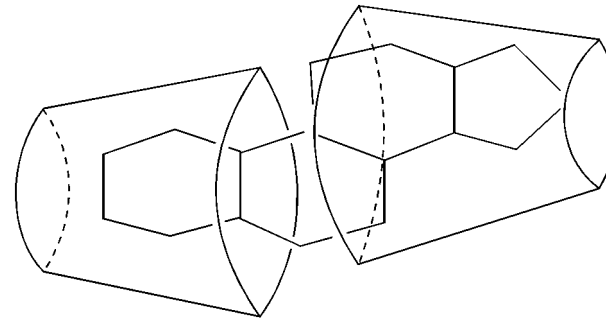

Figure 3 Schematic picture of the clathrate formation of a steroid by two β-cyclodextrin molecules.

• Number of solid-state forms
• Hygroscopicity
• Chemical stability
• Reproducible production
• Pharmacokinetics (dissolution rates)
• Toxicological properties
• Comminution
• Stability against excipients

Figure 4 Properties of the different solid-state forms of a drug to be considered when choosing the optimum form to be used in the final product.

development of the crystallization process of a drug. The form, once decided upon, has to be used in all relevant clinical and pharmaceutical tests and it must be certain that this form can be crystallized in a reproducible way, and that it can be formulated into the drug product.

A number of basic physico-chemical and pharmaceutical properties of the different forms that are considered for selection are listed in **Figure 4**, and can be tested and used in the process of decision making.

A drug substance that occurs only in a single polymorphic form is preferred; if not available, the stable polymorph is preferred. The techniques to infer the relative stability of polymorphs include solubility measurements, storage in suspensions and DSC experiments to construct enthalpy–temperature diagrams.

Crystal size and habit

Crystal size and habit of a drug can vary considerably. Thin needles, platelets and rhombohedral crystals are found. The crystal habit can influence all processes after crystallization

- during work-up, the de-watering in the centrifuge, the washing of the filter cake and the drying are affected;
- in the formulation, behaviour during micronization or flow during direct tableting are affected.

Micrographs of the drug substance and crystal size distributions can help in understanding the behaviour of the product crystallized under different conditions.

Habit The external appearance of crystals is called habit. The crystal habit can be influenced by the growth conditions. For example, crystals of the A modification of Abecarnil, a β-carboline derivative, grown after spontaneous nucleation at high supersaturations exhibit an avicular habit, while those grown at moderate supersaturations after seeding are still needle like but thicker and more rod-like (**Figure 5**).

Other factors determining the crystal habit are the solvent and the impurity profile of the material to be crystallized. The impurity level that influences the habit – and other properties – can be as low as ppm. **Figure 6** shows the habits of a steroid crystallized from two different solvents, one more protic (solvent I) and the other more aprotic (solvent II). Of course, the different habits lead to a different behaviour in downstream processing.

Crystal size distribution For the formulation of oral dosage forms, the desired crystal size distribution is

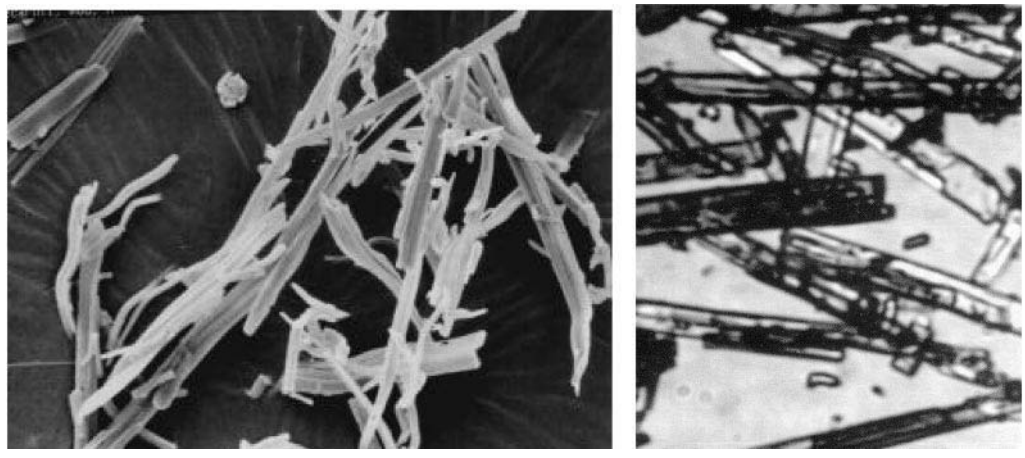

Figure 5 (See Colour Plate 111) Habit of Abecarnil grown from methanol after spontaneous nucleation at relatively high supersaturations (left) and grown at moderately low supersaturations after the addition of seeds (right).

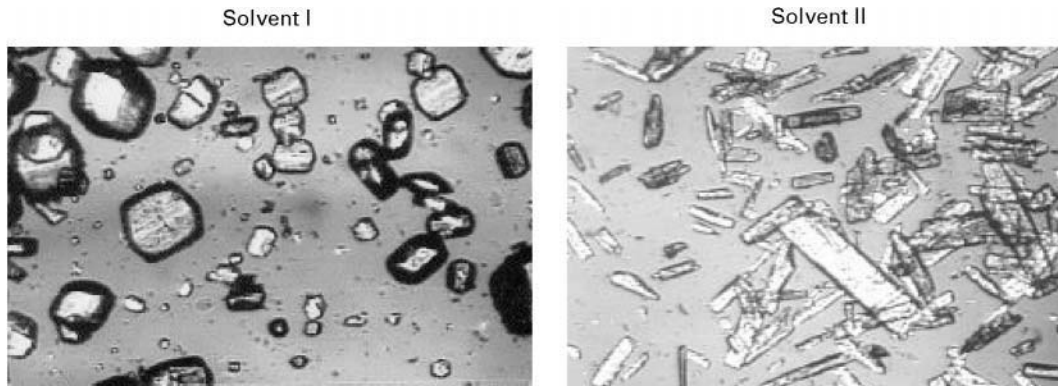

Figure 6 (See Colour Plate 112) Habit of a steroid crystallized from two different solvents.

mainly imposed by the demands for blend and content uniformity. For low-dosage formulations, such as steroids in contraceptives, the maximum crystal size is $\leq 10\,\mu m$. These crystal sizes cannot be attained via classical crystallization techniques. Thus, the standard procedure is crystallization and drying followed by a comminution, e.g. via jet-milling. It has been reported that the milling process is also dependent on the crystal size and the homogeneity of the crystal size to ensure a homogeneous milling process.

The size distribution obtained in a jet mill is decisively determined by the cut size of the cyclone of the mill. When the drug substance is to be used without comminution, the crystal size distribution will typically be broader. Small crystals, ≤ 10–$100\,\mu m$, can only be achieved via precipitation, larger crystals by evaporative or cooling crystallization. If large crystals are desired, the best way to control the process is via seeding. Here, care must be taken not to destroy the crystals during the crystallization process through the power input of the stirrer or during work-up, especially in agitation dryers.

Care must be taken to avoid agglomeration during crystallization and drying, as this process is erratic and in precipitation processes agglomeration is almost unavoidable. For the formulation of liquid dosage forms, the dissolution rate can limit the permissible crystal size, although the requirements are not really strict.

Development of the Crystallization Process

In most cases, a drug substance will be crystallized from solution in a batch process. The techniques most often employed are cooling, evaporative, drowning-out and reaction crystallizations. Glass-lined as well as stainless-steel vessels are used. These classical crystallization techniques and their implications will be discussed in detail. Certain properties of the drug substance may call for a crystallization from the melt, via spray drying or through the use of novel techniques for particle formation. These techniques will be discussed more briefly later.

Laboratory Development of Crystallization Technique

Supersaturation, nucleation and growth The crystallization involves two basic steps, nucleation and growth. The driving force for both processes is the relative supersaturation, typically defined as $\sigma = \Delta c/c_{sat}$, where $\Delta c = c - c_{sat}$, the difference between the actual concentration c and the saturation concentration c_{sat}. Depending on the magnitude of the supersaturation, at which the nucleation occurs, nucleation and growth will have different importance:

- at high supersaturation, nucleation will be the dominant process, the number of nuclei formed is large so that the increase in size via growth and thus the particles found are small;
- at low supersaturation, the number of nuclei is small so that growth dominates and coarse crystals will be obtained.

The first process is usually called precipitation, the second one crystallization. In both processes, nucleation can either be deliberate by seeding or involuntary by primary, spontaneous nucleation. As far as spontaneous nucleation concerned, heterogeneous nucleation by foreign particles in the solution will dominate. In case of easily or moderately soluble substances secondary nucleation caused by addition of the parent crystals in general dominates the nucleation process, once crystals of a sufficiently large size are present.

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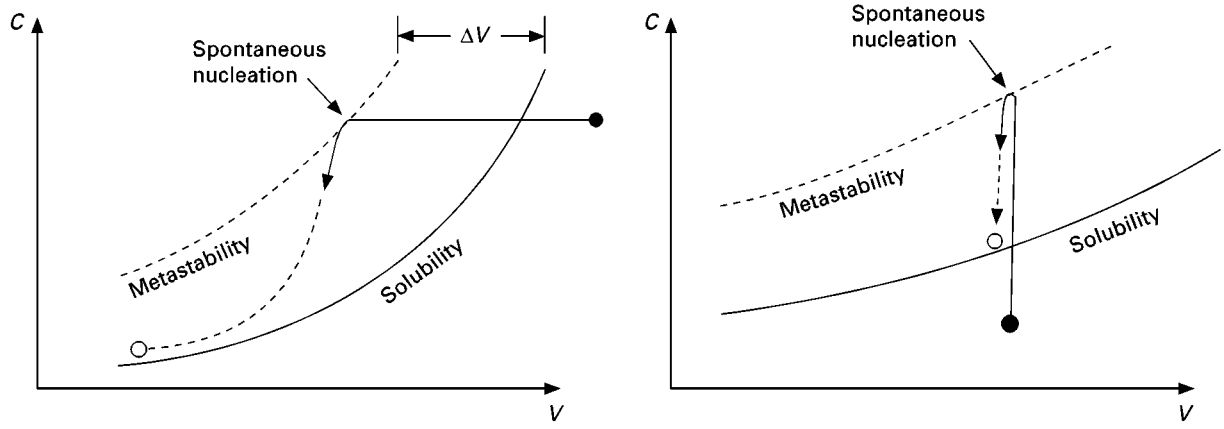

Figure 7 Typical solubility and metastability curves for a drug substance.

Solubility and metastability Two basic pieces of information on the system are necessary for a successful development of a crystallization process, the solubility curve and degree a solution can be supersaturated before spontaneous nucleation occurs.

The solubility defines the equilibrium state of the substance dissolved in the mother liquor, and the metastable zone is a concentration region, where a supersaturated mother phase can exist for a certain period of time without spontaneous nucleation. This latter region has typically a width of the order of 10°C and owing to the relatively large metastable zone, the amount of material coming out of solution under spontaneous nucleation without further cooling can be of the order of 10–30% of the entire mass, which is a considerable value. **Figure 7** shows typical solubility curves and metastable lines. The left-hand system lends itself to cooling crystallization, the right hand one to a evaporative crystallization because of the slope of the solubility curve.

For a drowning-out crystallization, a primary solvent in which the drug substance has a high solubility and a secondary, or anti-solvent, which has a negligible solubility are needed. **Figure 8** shows three typical curves for the mixing.

If the solubility has a concave curvature, i.e. the secondary solvent acts as an anti-solvent a drowning-out crystallization is feasible as shown in curve B. For curves A and C, crystallization by addition of an anti-solvent is not possible.

For precipitation by mixing of reactants or the formation of salts, the solubility is given by the solubility product, i.e. a + b → product↓ and $K = [a]\,[b]$ (**Figure 9**).

For moderate formation constants, the solubility at [a] = [b] is quite low. This implies high to very high supersaturations upon mixing, which can lead to small or very small crystals, which in turn can cause problems in downstream processes, $\sigma = \Delta c/c_{eq}$. If c_{eq} is very low, σ will become very high. But this on its own has nothing directly to do with small crystals. Small crystals result from the lack of growth limits in the solution (even at high σ values). Apart from that abundant nucleation also leads to small crystals, but this is also true for easily soluble compounds.

Influence of impurity and purity of material An often underestimated effect is caused by changes that may be made during the lifetime of the synthesis and its implications for the crystallization process. Variations in the impurity profile can influence both the width of the metastable zone and thus the degree of supersaturation at which spontaneous nucleation occurs, and the polymorph obtained during via spontaneous nucleation. It can also influence the rate of polymorphic transformation during work-up and the habit and crystal size. Although the effects of a changing impurity level on the behaviour of a drug substance are difficult to anticipate during the first stages of development, there is a need for a careful investigation of these effects.

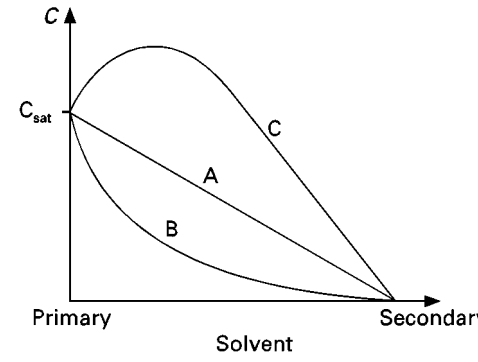

Figure 8 Typical solubility curves for a drug substance in a mixture of a primary and a secondary solvent.

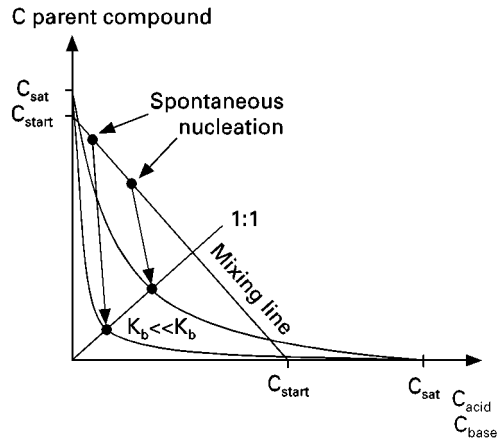

Figure 9 Solubility for a ionic reaction crystallization such as the formation of the salt. The supersaturation at moderate formation constants reaches a high value.

Choice of solvent and of the crystallization technique The choice of solvent for the crystallization of a drug substance is governed by (i) the need to use a Class 3 or Class 2 solvent and (ii) a solvent that does not interact with the drug substance. These considerations limit the solvents allowed to very few, preferably such as ethanol, ethyl acetate and water.

A cooling crystallization is the first choice, if the temperature dependence of the solubility permits it. It is the most straightforward technique for the crystallization, as the temperature, is easily controlled. In most cases, the temperature dependence will be such, that >90–95% of the material dissolved will crystallize upon cooling from a temperature close to the boiling point down to ambient temperatures. Final temperatures down to $-10^{\circ}C$ can easily be handled; lower temperatures may significantly increase production costs.

If the solubility changes only gradually with temperature, evaporative crystallization, either at ambient or at reduced pressure may be chosen. To increase yield it is often followed by a cooling step.

If the solubility of the drug in the organic solvent is high, and if the solvent cannot be changed and it is miscible with water, anti-solvent precipitation with water can be used. Since a drowning-out crystallization leads to solvent mixtures that have to be treated afterwards, this technique should be avoided when possible.

Rate of crystallization The rate of crystallization should not exceed values that cause too much uptake of solvent via inclusions. For a cooling crystallization, natural cooling profiles should be avoided, as most of the material crystallizes too fast. Linear cooling rates are a first approximation. The rates can be classified as slow, realistic, fast and crash cooling for rates of <5, <10, <15 and $>15^{\circ}C\,h^{-1}$, respectively.

Instead of linear rates, a controlled rate of crystallization should be used where possible; this is especially important for drowning-out crystallizations, for neutralization reaction crystallizations or for the formation of salts. In these cases, even a moderate dosage of the anti-solvent or the acid or base can lead to very high supersaturation which in turn can cause the formation of oils or amorphous material. Often most of the yield is produced during the addition of the first amount of the secondary solvent.

Thus either a very slow dosing or when exactly stepwise dosing with time interval between are appropriate tools to avoid too high supersaturation and the adverse effects usually observed for nucleation and growth at high supersaturation.

At the point of addition, high local supersaturation is generated so that mixing has to be optimized (see **Figure 10**).

Programmes for cooling, evaporative and drowning-out crystallization are derived by requiring the crystallization to proceed with a constant rate of deposition of mass or with a constant linear growth rate. **Figure 11** presents curves for a drug substance having a temperature dependence of the solubility of $40\,kJ\,mol^{-1}$. The solubility decreases by a factor of 10 with a change in temperature from 70 to 20°C. However, the calculations yield only the profile, the absolute times are not given.

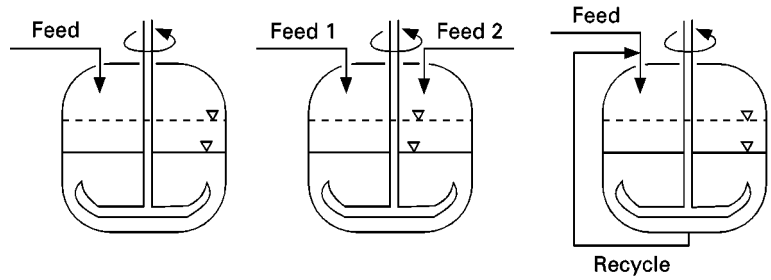

Figure 10 Mixing schemes for precipitation. Dosing of the anti-solvent into the primary solvent (left) is to be avoided. A parallel dosing of both solutions (middle) is better and even better is a dilution scheme (right).

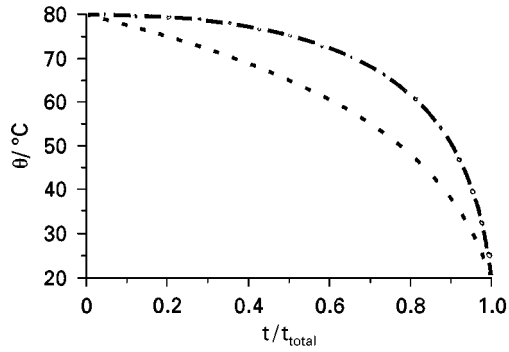

Figure 11 Suggestion for a cooling programme for a drug having a high solubility dependence on temperature. The lower curve is for a constant flux of mass, the upper for a constant rate of crystallization. –◦– Constant growth rate; – – – Constant flux of mass.

Seeding is more likely to succeed for cooling and evaporative crystallizations but rather difficult in drowning-out crystallizations, or in precipitation because these processes are dominated by primary nucleation around the inlets that can hardly be avoided.

Scale-up Crystallization parameters arrived at in the laboratory have to be scaled up for production and this must always be borne in mind. In the laboratory, typically glassware or small crystallization vessels are used. In production, vessels are either glass or glass lined, or are made of stainless steel. The vessels are equipped with a cooling/heating jacket and a distillation device. Stirrers are normally impellers or of the anchor type. Few vessels are baffled, the only device acting in this respect is often the temperature probe.

The scale-up factors from laboratory to production are in the order of $100\,mL^{-1}\,L$ to several 100 L or 1000 L, factors considered high for crystallization operations. The stirrer action can be scaled up using either constant tip velocity or constant power input, as is the case for all crystallization operations.

A problem often encountered in production but seldom in the laboratory is the formation of encrustation during distillation. This is to be avoided, as it can create hot spots and can act as a source of seeds. In this case, the outcome of the crystallization is entirely unpredictable. Encrustations during distillations can be avoided using reflux schemes.

Work-up The classical procedure for the work-up of the crystallized drug substance is centrifugation and washing followed by drying on a tray dryer. This procedure involves a number of transfer steps, where the product can be contaminated or where the product can contaminate the environment.

The number of transfer steps can be minimized by using the filter type dryer shown in **Figure 12**. The device is used for the solid–liquid separation, washing and finally drying. The heat is transferred both through the outer wall and the stirrer. The stirrer facilitates the washing and the drying. However, if this stirrer is used inappropriately, it can act as a milling device and can generate fines down to $<10\,\mu m$.

Other Crystallization Techniques

Direct contact cooling (DCC) In the direct contact cooling (DCC) process a solution of the drug substance in a primary solvent at a temperature close to saturation is mixed with a liquid coolant, rapidly creating supersaturation, consequently followed by crystallization of the drug substance. Coolants include immiscible as well as miscible liquids and liquidified gases. Recently, solid CO_2 at $-60^{\circ}C$ has been used as coolant. Coolants that are gaseous under ambient conditions offer the advantage that they can easily be separated from the mother liquor. Depending on the heat capacities and the ratio of mixing very high supersaturations and thus fine particles can be obtained. **Figure 13** shows a SEM micrograph of Abecarnil crystallized by using solid CO_2 coolant.

Spray drying In spray drying, a solution of the drug substance in an appropriate solvent is sprayed into

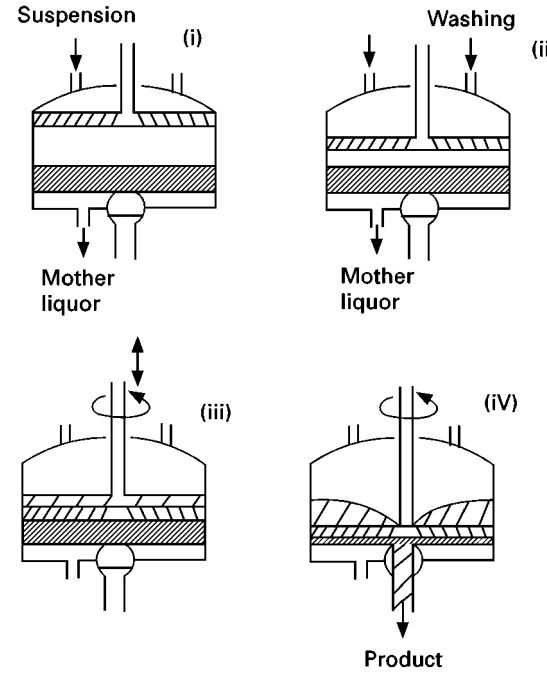

Figure 12 Schematic drawing of a filter dryer, in the states (i) solid–liquid separation, (ii) washing and (iii) drying. The heating is via both the surface of the dryer and the stirrer and (iv) product discharge.

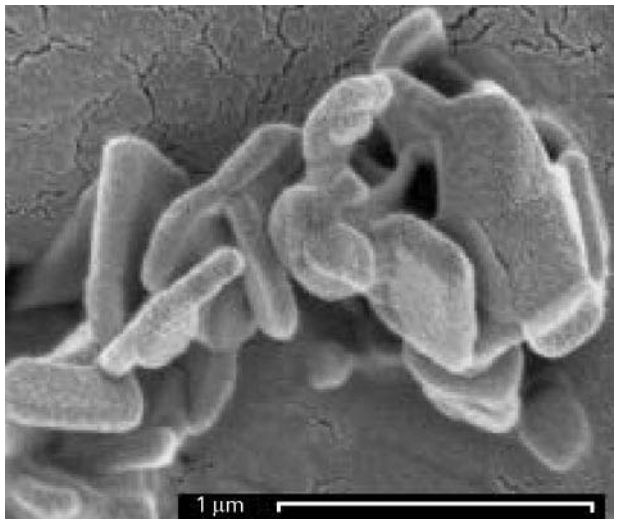

Figure 13 SEM image of Abecarnil obtained by using solid CO_2 as direct contact coolant.

a hot stream of gas that carries the heat both for the evaporation of the solvent and the drying of the product. Although the temperature of the gas stream lies between 200 and 300°C, the maximum temperature that the drug substance is exposed to is close to or less than the boiling point of the solvent. The short residence times also limit the thermal stress.

The particle size attained through spray drying is of the order of micrometres. The habit of the particles obtained strongly depends on the system, typical particle shapes are shown in **Figure 14**. The left micrograph shows well-defined spherical particles, that are fully separated. The right micrograph shows felted needles obtained with a different substance.

In most cases, spray drying will be from organic solvents. In these cases, safety against explosions can be achieved either by keeping the amount of solvent in the stream of air below the explosive limit or by using nitrogen as an inert drying gas.

The solid-state form obtained can be amorphous or crystalline depending on the substance and the drying conditions. The fast evaporation of the solvent can lead to amorphous material. However, if the glass transition temperature of the drug substance is less or equal to the temperature regime in the dryer, a transformation into a crystalline product may occur. This transformation may be facilitated by residual amounts of solvent.

Melt crystallization Melt crystallization techniques are rarely applied for the crystallization of drug substances, as many have a high melting point, typically ≥ 150°C, a temperature at which these compounds have a tendency to become unstable if exposed to these temperatures for prolonged periods of time.

Techniques of particle formation The requirement to produce small particles of a drug substance has led to the development of alternative processes of particle formation via a precipitation technique. These processes are as follows:

- RESS: the Rapid Expansion of Solutions of the drug in Supercritical CO_2, or other fluids. This technique is hampered by the low solubility of most drug substances in supercritical fluids. Although modifiers can increase the solubility, they have to be removed effectively to prevent agglomeration or ripening.

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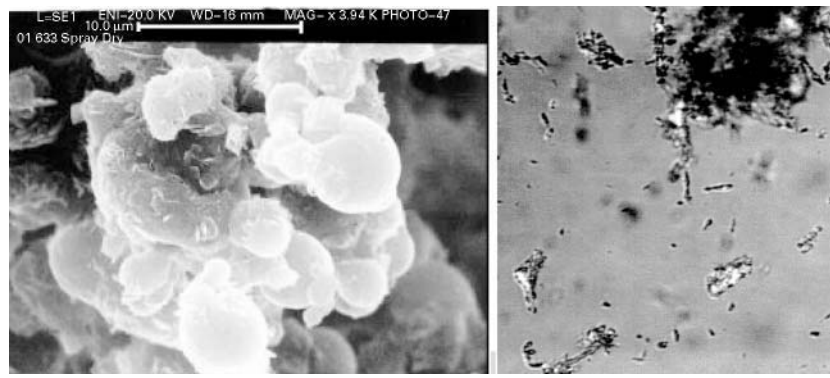

Figure 14 (See Colour Plate 113) Shape of particles obtained via spray drying. The left micrograph shows well-separated spherical particles typically obtained. Note the indentations on one side. The right micrograph shows felted needles that are in addition interwoven. Both products are fully crystalline.

- PCA: the precipitation of the drug substance from a solution in a primary solvent with the aid of a Compressed Anti-solvent, namely CO_2.
- SEDS: Supercritical solution Enhanced Dispersion of Solutions. A solution of the drug in a primary solvent is mixed in a nozzle with a stream of supercritical CO_2 that acts both as dispersant and anti-solvent. The particles form immediately and are collected on filter plates. This technique offers a number of very intriguing advantages such as very small particle size, very low residual solvent contents, or a low surface charge of the particles facilitating the formulation process.

It has been reported, that proteins or peptides crystallized via this technique fully retain their biological activity.

With these processes, crystal sizes down to and below 1 μm can be attained. So far, all these processes work in batch mode with small batch sizes, although attempts are being made to increase the batch size.

The particle formation, nucleation and growth, in all three techniques is rapid. Information on the nucleation and growth process are only emerging and more work needs to be done. Due to the nucleation and growth under very high supersaturations, the polymorphic form obtained might not be the stable one.

Acknowledgements

The authors are indebted to a number of colleagues who helped during the years, namely W.H. Otto and M. Schirmer for their help in crystallization experiments. Other helpful colleagues include T. Backensfeld, S. Erb, P. Höfert, S. Küppers, G. Mann, R. Mertins, P. Nisch, M. Ottnad, R. Richter and G. Winter.

See Colour Plates 111, 112, 113.

See also: **II/Crystallization:** Control of Crystallizers and Dynamic Behaviour; Polymorphism. **III/Supercritical Fluid Crystallization.**

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Neutral and Acidic Drugs: Liquid Chromatography

R. K. Gilpin, Wright State University, Dayton, OH, USA
C. S. Gilpin, Ohio University, St. Clairsville, OH, USA

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Introduction

Although the general topic of the high performance liquid chromatographic (HPLC) analysis of neutral and acid drugs encompasses a broad range of compounds that include antibacterial agents to vitamin supplements, many of the more common acid compounds are therapeutically active as analgesics, antipyretics, and antiinflammatories (e.g., aspirin, diclofenac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamic acid, naproxen, tolmetin and other compounds shown in **Table 1**). In many cases, this group of compounds are relatively small molecules and are structurally simple, containing only one or two aromatic rings and a single ionizable carboxyl group. Many of the common